REMARKS

Entry of the foregoing and favorable reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, claims 2-13, 17 and 20-32 have been cancelled. Applicant reserves the right to file continuation applications and/or divisional applications directed to the cancelled subject matter.

Claims 1, 18, 19, 33, 38, 39 and 40 have been amended to further clarify the present invention. No new matter has been added. Accordingly, entry of the amendment is respectfully requested.

Claims 18 and 38 have been objected to as failing to further limit claims 1 and 33 respectively, on which they are dependent, on the ground that the recitation "biological sample" is defined in the specification as a "body fluid".

Applicants submit that the recitation "biological sample" is not limited to body fluids. Paragraph [0034] of the specification also teaches "[a] biological sample can be a tissue removed from an individual." Thus, claims 18 and 38 have been amended to further define the "biological sample" as a "body fluid", and claims 19 and 39 (which are dependent on claims 18 and 38 respectively) have been amended to further define the "body fluid" in terms of various fluids. Reconsideration and withdrawal of the objection are respectfully requested.

Claims 33-39 have been rejected under 35 U.S.C. §112 first paragraph, as being non-enabling for a decreased level of diglycosylated pyridinoline.

Claim 33 has been amended in order to recite that an increased level with respect to the reference level is indicative of the presence of a synovial disease. Support for

this amendment is set forth in the specification, *e.g.*, on pages 2 and 3, in paragraphs [0009], [0011], and [0013]. Therefore, withdrawal of this rejection is respectfully requested.

Claims 1, 13-19, 24 and 33-40 have been rejected under 35 U.S.C. §112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject-matter which applicant regards as the invention.

Claim 1 has been amended to recite that the level of the marker, measured in the sample from the individual, is compared to a reference level of the marker, wherein the reference level is a "previously measured level in the same individual." Support for this amendatory language is set forth in the specification, *e.g.*, on page 9, paragraph [0052].

The comparison of the measured level of the marker to a previously measured level of the marker in the same individual, clearly indicates that the sampling and measuring are conducted at different times, allowing for the monitoring of the evolution of the disease.

Claim 33 has been amended as mentioned above in order to recite that an "increased" level with respect to the reference level is indicative of the presence of a synovial disease.

Claim 24 has been cancelled, thus rendering the objection moot.

Claim 40 has been rejected on the ground that the recitation "mention of a reference level" renders the claim unclear as to what applicant intends. This claim has been amended to delete "mention of".

In view of the foregoing amendments, reconsideration and withdrawal of each ground of rejection are respectfully requested.

Claims 24 and 40 have been rejected under 35 USC 103(a) as being unpatentable over Robins, *et al.* (international patent application WO89/12824)("*Robins*") in view of U.S.

Patent 4,444,879 to Foster, *et al.* ("*Foster*"). Since claim 24 has been cancelled, the rejection is considered moot as to that claim, and will be addressed to the extent that it applies to claim 40. For the following reasons, this rejection is respectfully traversed.

The Examiner has alleged that *Robins* discloses the measurement of glycosylated pyridinoline, and the use of antibodies directed towards diglycosylated pyridinoline used in immunoassays, and that the only differences with the present claims lie in the packaging into a kit and in the reference level. In the Examiner's view, these differences would have been obvious in view of *Foster*.

Robins, *et al.* does not disclose antibodies directed toward **di**glycosylated pyridinoline used in immunoassays. Indeed, *Robins* discloses the separation of mono and **di**glycosylated pyridinoline. Independently, *Robins* also discloses a general protocol for obtaining antibodies. It can thus not be concluded that Robins et al specifically discloses antibodies directed toward **di**glycosylated pyridinoline used in immunoassays.

Moreover, the Examiner has acknowledged that *Robins* fails to mention a reference level representing the absence of synovial disease. This difference is important. The lack of disclosure or suggestion in *Robins* of a reference level of **di**glycosylated pyridinoline representing the absence of a synovial disease is understandable, because:

- it was not even suspected that diglycosylated pyridinoline (Pyr-Gal-Glc) could be indicative of a synovial disease; indeed, as mentioned in the previous response, *Robins* does not disclose that disaccharide derivatives of hydroxylysine can be used as a specific marker for diagnosing a synovial disease,

- the presence of Pyr-Gal-Glc was thought to be indicative of bone or cartilage degradation (see *Robins*, page 6, lines 15-16) and not of synovium.

The prior art teaches that bone, cartilage and synovium are distinct tissues. Paragraph [0132] and figs. 5 and 6 of the present specification teach that the type of glycosylated pyridinoline molecule differs in these three tissues - in synovial fluid, glycosylation is of the Gal-Glc type (*i.e.*, diglycosylated), that of bone is of the Gal type, and the cartilage appears to be only slightly dlycosylated. Thus, bone or cartilage cannot be said as equivalent to synovium. Since *Robins* expresses the belief that the presence of Pyr-Gal-Glc was indicative of bone or cartilage degradation, Applicants submit that *Robins* teaches away from the claimed invention.

Therefore, the insertion in the kit of a reference indicating the limit upon which the measured level of Pyr-Gal-Glc is indicative of a synovial disease was absolutely not disclosed in *Robins* and the skilled artisan would not have found any motivation, on the basis of the teachings in *Robins*, to prepare the kits of claim 40.

The secondary reference, *Foster*, does not remedy the deficiency of the primary reference. *Foster* does not disclose or suggest the insertion in the kit of a reference indicating the limit upon which the measured level of Pyr-Gal-Glc is indicative of a synovial disease. This reference is unrelated to the domain of synovial disease.

Therefore, the collective teachings of *Robins* and *Foster* fail to render the subject matter of present claim 40 obvious. There is no teaching or suggestion in the collective prior art teachings that diglycosylated pyridinoline is a marker *specific for synovial disease* such that a diagnostic kit can be made by incorporating a means for measuring diglycosylated pyridinoline

and a reference level representing the absence of the disease for comparison.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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